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# Early-onset colorectal cancer risk extends to second- and third-degree relatives

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## Abstract

**Introduction.—**Family history is a risk factor for colorectal cancer (CRC), however whether family history also contributes to non-syndromic early-onset CRC is unknown.

**Methods:** We estimated risk to first-, second-, and third-degree relatives of early-onset CRC cases in the Utah Pedigree Database.

**Results:** We observed elevated risks beyond RR=2.0 for early-onset CRC among first- and second-degree relatives of early-onset CRC cases, with RRs of 6.0 and 3.1, respectively.

**Discussion:** Relatives of early-onset CRC cases are at higher risk of both early-onset CRC and CRC at any age, and the location is not necessarily similar to the affected relative.

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## INTRODUCTION

Family history, an important non-modifiable colorectal cancer (CRC) risk factor, has been harnessed for use in targeted cancer screening programs for earlier CRC detection. Incidence is rising for early-onset colorectal cancer (EO-CRC) (1). There is a paucity of literature on the risk to relatives of early-onset CRC (2,3), generally defined as prior to age 50 years, outside of familial syndromes. We examined risk, as well as location, of CRC and EO-CRC in first- second-, and third-degree relatives (FDR, SDR, TDR) of EO-CRC cases.

## METHODS

Complete methods are available in the Supplementary Digital Content. We utilized the Utah Population Data Base (UPDB) to study Utah founder genealogies with more than three generations that are linked to the Utah Cancer Registry (UCR). All CRC cases with linked genealogy data in the UCR were included here, including syndromic cases which were not specifically identified in UPDB. Early-onset CRC was defined as that diagnosed ≤age 50 years, and included 1,510 EO-CRC cases (1,168 left-sided).

Relative risks (RR) for a specific CRC phenotype in a group of relatives was estimated as the observed number of CRC cases divided by the expected number of cases given UPDB disease rates. The observed number of cases among all relatives (e.g. FDRs) with the specific CRC phenotype (e.g. EO-CRC cases) were counted without duplication. The expected number of cases among all the specified relatives was estimated by summing the cohort-specific rate of each relative.

We performed the genealogical index of familiality (GIF) test for different sets of CRC cases, comparing the average pairwise relatedness of cases (e.g. CRC dx ≤50 years) with the expected pairwise relatedness for a set of matched individuals in the UPDB (4).

## RESULTS

Table 1 shows the estimated RRs for EO-CRC for FDRs, SDRs, and TDRs of the 1,510 EO-CRC cases. FDRs of EO-CRC cases are six times more likely to be diagnosed with EO-CRC, SDRs are 3.09 times more likely, and TDRs (primarily first cousins) are 1.56 times more likely.

Table 1 also shows the estimated RRs for CRC at any age, and for left- and right-sided CRC (at any age) among relatives of the 1,510 EO-CRC cases. Individuals are at 2.64-fold higher risk of CRC at any age if they have a FDR with EO-CRC, at 1.96-fold higher risk if they have a SDR with EO-CRC, and 1.3-fold higher risk if they have a TDR with EO-CRC. The risk for EO-CRC is higher than the risk for CRC at any age, for all degrees of relatives shown (e.g. RR=6.00 vs 2.64 for FDRs).

Significantly elevated risk for CRC at both locations (left or right) was observed for all degrees of relationship; however the confidence intervals are overlapping, suggesting no difference in risk of left- vs right-sided CRC.

The GIF test estimated mean pairwise relatedness for the 1,510 cases (4.06), and shows significant excess relatedness beyond what would be expected within the UPDB (mean 2.76, $p<0.001$), even when first- and second-degree relationships were ignored (2.95 compared to 2.55, $p<0.001$).

## DISCUSSION

We observed elevated risk of EO-CRC among FDRs, SDRs, and TDRs of EO-CRC cases, and two independent methods (RRs and GIF) both lend support for the hypothesis that EO-CRC cases cluster more than expected. Our study suggests that FDRs and SDRs of EO-CRC cases are themselves at higher risk for CRC at any age, with RRs of 2.64 and 1.96, respectively, which approximates sibling recurrence risk estimates for CRC at any age (5). TDRs are also at higher risk of EO-CRC and overall CRC. Finally, our study indicates that relatives of EO-CRC cases are no more likely to develop CRC on the right than the left side of the colon; therefore colonoscopy remains a preferable tool over flexible sigmoidoscopy in these individuals.

Our findings may in the future influence future CRC screening recommendations for individuals with family history of EO-CRC. Clinically, there are no screening guidelines for SDRs or TDRs of EO-CRC cases unless Lynch syndrome or another genetic condition is identified. Our findings suggest that early colonoscopy screening may be considered not only in FDRs, but also in SDRs and possibly TDRs of EO-CRC cases. Relatives may also benefit from an evaluation with genetic counseling to assess underlying inherited conditions. However, we note that there are important considerations in the need for resources to accomplish earlier population-based CRC screening (6).

Two studies evaluated risk to relatives of EO-CRC cases; however for FDRs only. In a Finland cohort, higher risk for siblings of CRC cases diagnosed <40 (without an affected parent) was reported, with a standardized incidence ratio of 5.29 (3). Another study reported higher risk in siblings (RR=2.67 compared to parents) in a sample of 267 microsatellite stable early-onset (<50 yr) CRC probands (2).

Our study is in contrast to Schoen et al which reported that having one FDR with early-onset CRC (<60 years) was not associated with higher CRC risk (7).

A strength of our study is the extensive genealogy data in the UPDB, a large and unique resource that allows for unbiased evaluation of risk out to TDRs (uncommon even in large cohorts). Further, all CRC cases are histopathologically confirmed in the UCR, therefore misclassification of CRC and recall bias is minimized.

An important weakness herein is the inclusion of primarily individuals with Northern European ancestry, limiting generalization to other racial/ethnic groups. Approximately 8-13% of EO-CRC cases (of European ancestry) have Lynch syndrome (8–10) and approximately 1 in 279 individuals in the general population carry a Lynch syndrome-associated mutation (11). We were unable to identify and exclude individuals with inherited syndromes; however, we do not believe that Lynch syndrome is the primary driver for our findings since the majority of EO-CRC cases were left-sided (n=1,168; 77.4%) and Lynch

primarily occurs in the proximal colon. In fact, there are more right-sided cases (approximately 40%) in individuals above age 50 in the UPDB sample. In spite of this limitation, we believe that our sample represents a real-world scenario faced by clinicians.

Our study supports consideration and further study of early surveillance of extended relatives of EO-CRC cases to ultimately prevent CRC-associated morbidity and mortality.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Highlights

- While it is recognized that family history is associated with higher colorectal cancer (CRC) risk, it is not clear to what degree having a family history of early-onset CRC (before age 50) contributes to risk and whether risk extends beyond first-degree relatives.
- Our study suggests that first-, second-, and third-degree relatives of early-onset CRC cases are at higher cancer risk for both early-onset CRC and CRC at any age.
- The findings suggests that extended family history should be part of the discussion when making cancer screening decisions.

**Table 1.**

Estimated risk of early-onset CRC, CRC at any age, and any age left- and right-sided[1] CRC among different relative types of n=1,510 early-onset CRC cases in the UPDB

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| Relative | Phenotype in relative | N | Observed | Expected | RR (95% CI) |
|---|---|---|---|---|---|
| First degree | CRC <50 yr | 11,912 | 64 | 10.7 | 6.00 (4.62, 7.66) |
| | Any age CRC | | 293 | 111.1 | 2.64 (2.34, 2.96) |
| | Any age left-sided CRC | | 197 | 72.7 | 2.71 (2.34, 3.12) |
| | Any age right-sided CRC | | 121 | 45.2 | 2.67 (2.22, 3.20) |
| Second degree | CRC <50 yr | 37,023 | 61 | 19.7 | 3.09 (2.37, 3.97) |
| | Any age CRC | | 554 | 282.3 | 1.96 (1.80, 2.13) |
| | Any age left-sided CRC | | 383 | 187.2 | 2.05 (1.85, 2.26) |
| | Any age right-sided CRC | | 218 | 116.7 | 1.87 (1.63, 2.13) |
| Third degree | CRC <50 yr | 98,192 | 78 | 50.0 | 1.56 (1.23, 1.95) |
| | Any age CRC | | 898 | 692.4 | 1.30 (1.21, 1.38) |
| | Any age left-sided CRC | | 584 | 457.7 | 1.28 (1.17, 1.38) |
| | Any age right-sided CRC | | 383 | 288.2 | 1.33 (1.20, 1.47) |

[1] Left-sided CRC includes splenic flexure, descending colon, sigmoid colon, rectosigmoid junction and rectum; right-sided CRC includes cecum, ascending colon, hepatic flexure and transverse colon.